Introductory Remarks: Overview of NDA 207,500 and 207,501

Isavuconazonium

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FDA

Anti-Infective Drugs Advisory Committee Meeting
January 22, 2015

Product: Cresemba® (Isavuconazonium)

- Pro-drug of Isavuconazole, a Triazole Antifungal Agent
- Applicant: Astellas Pharma US, Inc.
- NDA 207,500
  - Capsules (Equiv. to 100 mg Isavuconazole)
- NDA 207,501
  - Vials for Injection (Equiv. to 200 mg Isavuconazole)
- Proposed Indications
  - Invasive Aspergillosis
  - Invasive Mucormycosis
- Orphan Drug Designation for Proposed Indications

Clinical Trials

- 9766-CL-0104

Invasive Fungal Disease Caused by *Aspergillus* Species or Other Filamentous Fungi

  - Randomized
  - Double-Blind
  - Comparator: Voriconazole
  - Non-Inferiority Design

Main Source of Data to Support Aspergillosis Claim

Clinical Trials

- 9766-CL-0103
  - Patients with Renal Impairment

    or
  - Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts, or Dimorphic Fungi
  - Open-Label
  - Prospective
  - No Concurrent Comparator (Historical Control)

Main Source of Data to Support Mucormycosis Claim

Outline for the Day

- Applicant Presentations
- FDA Presentations
  - Aspergillosis - Cheryl Dixon, PhD
  - Mucormycosis and Safety – Edward Weinstein, MD, PhD
- Open Public Hearing
- Questions to the Committee/Committee Discussion

Question 1

- VOTE: Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of invasive aspergillosis?
  - If yes, provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed?

Question 2

- VOTE: Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of mucormycosis?
  - If yes, provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed?

Clinical Efficacy of Isavuconazonium for the Treatment of Invasive Aspergillosis

Cheryl Dixon, Ph.D.
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Outline

- Phase 3 Trial 9766-CL-0104
  - Design
  - Non-inferiority Margin
  - Patient Disposition/Demographics
  - Efficacy Results
  - Conclusions

Trial 9766-CL-0104 Design

- A Phase 3, double-blind, randomized trial to evaluate the safety and efficacy of isavuconazonium versus voriconazole in the treatment of invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi

- Patients randomized 1:1 to receive either isavuconazonium or voriconazole and stratified by
  - Geographic location (United States/Canada, Western Europe/Australia/ New Zealand, and Other Regions)
  - Prior allogeneic bone marrow transplant (BMT) status
  - Uncontrolled malignancy at baseline

Trial 9766-CL-0104 Design (cont.)

- Independent Data Review Committee (DRC) adjudicated:
  - the categorization of each patient's IFD at enrollment
    - proven, probable, possible, no IFD/no invasive mold infection
  - the patient's clinical, mycological, radiological, and overall response at End of Treatment (EOT), Day 42, and Day 84

- Primary Endpoint: All-cause mortality through Day 42
- Key Secondary Endpoint: DRC-assessed overall response at EOT

Analysis Populations

- Intent to Treat (ITT): all randomized patients who received at least 1 administration of study drug
- Modified ITT (mITT): proven or probable IFD as determined by DRC
  - using 2 consecutive serum galactomannan (GM) values ≥ 0.5 or at least 1 serum GM value ≥ 0.7 as defined in protocol
- mITT-FDA: proven or probable IFD as determined by DRC
  - using 2 consecutive serum GM values ≥ 0.5 or at least 1 serum or BAL GM value ≥ 1.0*
- Mycological ITT (myITT): proven or probable invasive aspergillosis

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420248.pdf

Non-Inferiority Margin

- **All Cause Mortality Through Day 42**
  - Prespecifed and justified margin of 10%
    - Original registration trial for voriconazole in which voriconazole was shown to be superior to amphotericin B for the treatment of aspergillosis

Voriconazole	Amphotericin B	Difference (95% CI)
27/144 (18.8) (12.7, **26.1**)	46/133 (34.6)	-15.8 (-26.1, **-5.5**)

    - Literature search to derive an estimate of placebo response (no treatment) as well as an historical estimate of amphotericin B response.

Placebo	Amphotericin B	Effect of Amphotericin B over Placebo
21/21 (**83.9**, 100)	82/137 (59.9) (51.1, **68.1**)	68.1-83.9= **-15.8**

Non-Inferiority Margin (cont.)

- **All Cause Mortality Through Day 42** (cont.)
  - Estimate of the Effect of Voriconazole Over Placebo (M1) for All-cause Mortality at Day 42

Direct (vori - placebo)	26.1-83.9=-57.8
Indirect [(vori - amphotericin B) +(amphotericin B - placebo)]	-5.5 + ½(-15.8)=-13.4

  - Therefore a non-inferiority margin of 10% based on clinical judgment for M2 is acceptable.
- **Overall Response at EOT**
  - Based on historical data available, an estimate for M1 for overall response at EOT cannot be derived.
  - The clinical interpretive criterion of 15% prespecified by the Applicant was determined to be acceptable.

Patient Disposition

	Isavuconazonium	Voriconazole
Randomized	263	264
ITT	258	258
mITT	143	129
Aspergillus species only*	49 (34.3)	39 (30.2)
Aspergillus species plus other mold species*	3 (2.1)	1 (0.8)
Non-Aspergillus species only	5 (3.5)	6 (4.7)
Mold species not otherwise specified (NOS)	14 (9.8)	15 (11.6)
No pathogen identified**	72 (50.3)	68 (52.7)
mITT-FDA	147	128
myITT	123	108
Probable by serum GM only	71 (57.7)	68 (63.0)
Proven or probable Aspergillosis by culture or histology	52 (42.3)	40 (37.0)

**A. fumigatus* and *A. flavus* were the most common pathogens identified.
**Probable based on GM with the exception of 1 isavuconazonium subject who was based on a culture from a non-sterile site and had adequate host factors and clinical and radiological factors

Patient Demographics (ITT)

- Generally balanced among treatment groups
  - Mean age 51 years
  - 60% male
  - 78% white
  - 11% US/Canada, 41% Western Europe/Australia/New Zealand, and 48% Other Regions
  - 20% prior allogeneic BMT
  - 70% uncontrolled malignancy at baseline

Results: All-Cause Mortality through Day 42

	Isavuconazonium	Voriconazole	Difference and 95% CI*
ITT**	48/258 (18.6)	52/258 (20.2)	-1.0 (-8.0, **5.9**)
mITT	28/143 (19.6)	30/129 (23.3)	-2.6 (-12.6, **7.3)**
mITT-FDA	28/147 (19.0)	28/128 (21.9)	-2.1 (-11.9, **7.7**)
myITT	23/123 (18.7)	24/108 (22.2)	-2.7 (-13.6, **8.2**)

*adjusted difference (Isa- Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status

**survival status unknown for only 3 isavuconazonium and 2 voriconazole ITT subjects. Treated as deaths.

Results: DRC-assessed Overall Response at EOT

	Isavuconazonium	Voriconazole	Difference and 95% CI*
mITT- Success	50/143 (35.0)	47/129 (36.4)	-1.6 (**-12.8**, 9.6)
Complete	17 (11.9)	12 (10.1)	
Partial	33 (23.1)	34 (26.3)	
Stable	42 (29.4)	33 (25.6)	
Progression	51 (35.7)	49 (38.0)	
mITT-FDA - Success	52/147 (35.4)	47/128 (36.7)	-1.8 (**-12.9**, 9.3)
Complete	19 (12.9)	14 (10.9)	
Partial	33 (22.5)	33 (25.8)	
Stable	43 (29.3)	34 (26.6)	
Progression	52 (35.4)	47 (36.7)	
myITT- Success	43/123 (35.0)	42/108 (38.9)	-4.0 (**-16.3**, 8.4)
Complete	13 (10.6)	12 (11.1)	
Partial	30 (24.4)	30 (27.8)	
Stable	36 (29.3)	29 (26.9)	
Progression	44 (36.8)	37 (34.4)	

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status

Efficacy Conclusions

- Non-inferiority of isavuconazonium compared to voriconazole, based on a 10% margin, was demonstrated for all-cause mortality through Day 42

- Similar rates of DRC-assessed overall response at EOT among isavuconazonium and voriconazole were observed

Clinical Efficacy of Isavuconazonium for the Treatment of Invasive Mucormycosis

and

Overview of Safety

Edward Weinstein, MD, PhD
Medical Officer
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Anti-Infective Drugs Advisory Committee Meeting
January 22, 2015

Clinical Efficacy for the Treatment of Invasive Mucormycosis

Outline

Study Design

Population Demographics

Patient Disposition

Outcomes

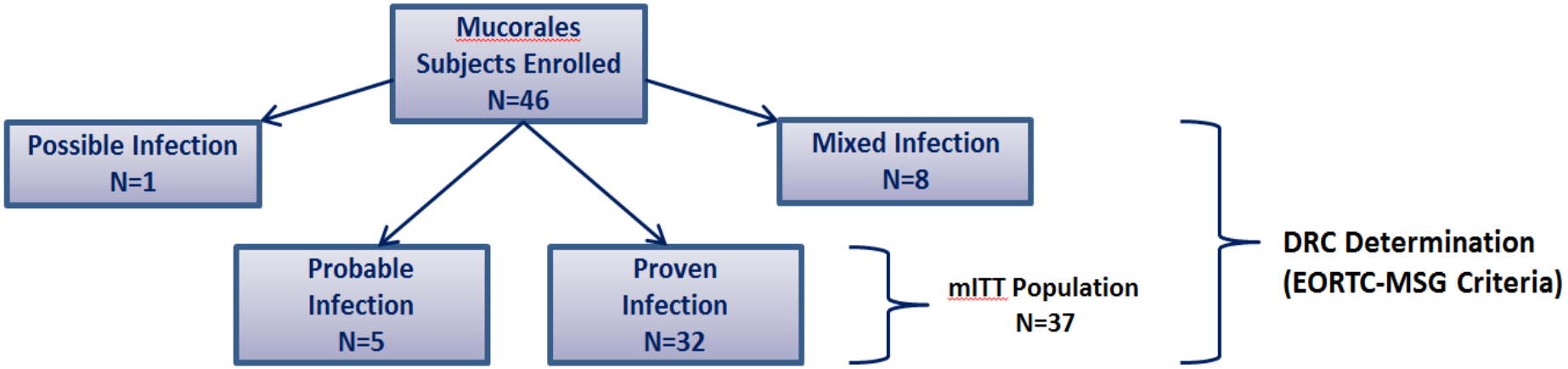
Comparative Analysis of Historical Control Populations

Study Design:

Trial 9766-CL-0103: Non-Comparative, Open-Label, Multi-Center

- Treatment of IA in Patients with Renal Impairment
- Invasive Fungal Disease Caused by Rare Molds, Yeasts or Dimorphic fungi

Population	N
Enrolled	149
Intent-to-Treat (ITT)	146
Modified Intent-to-Treat (mITT)	140
mITT-Mucorales	**37**
mITT-*Aspergillus*	24



Study Population Characteristics

Diagnosis and Treatment Group

Population Demographics

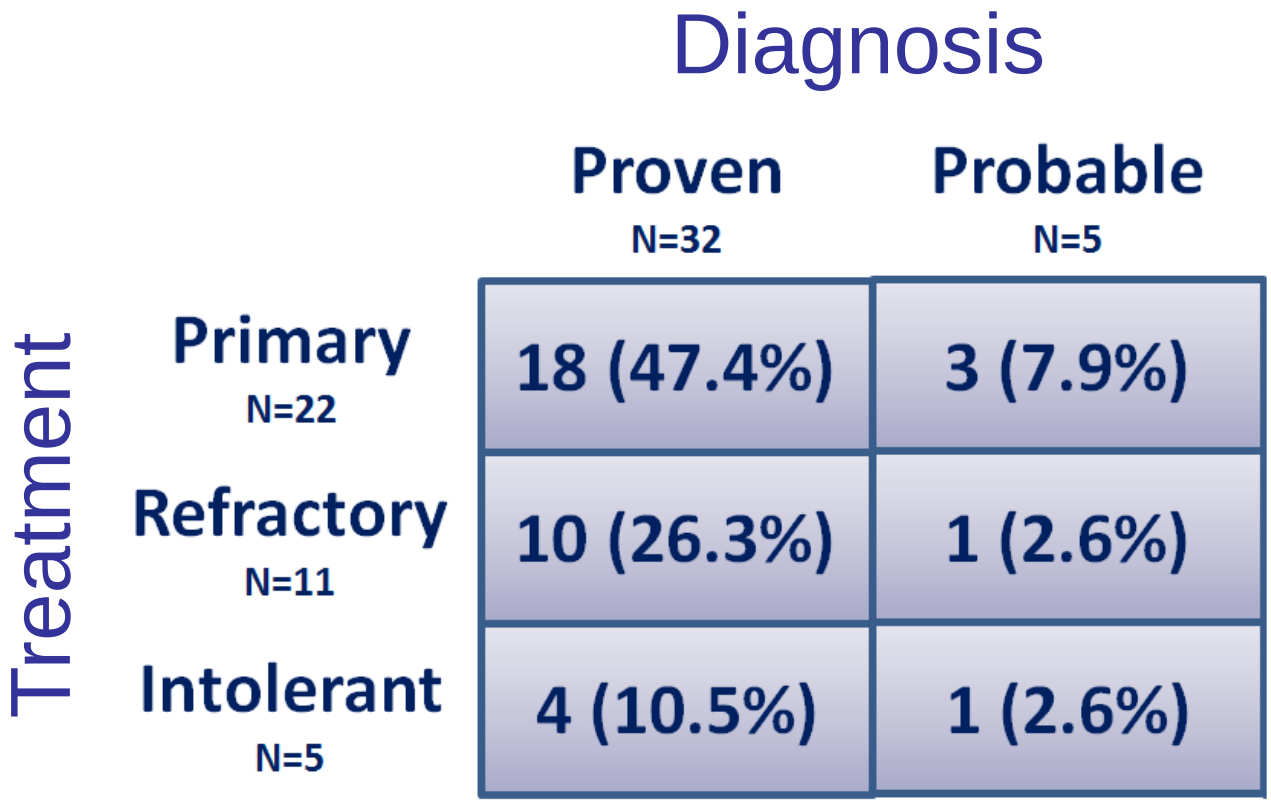
Host Factors

Identified Pathogen

Site of Infection

Population Demographics

Distribution of Mucorales mITT Patients per DRC: Infection Status and Treatment Group



Population Demographics

Parameter	Total (n = 37)
Age in Years, Mean (Range)	**49 (22-79)**
Gender	
Male	**30 (81.1%)**
Female	**7 (18.9%)**
Race	
White	**25 (67.6%)**
Black or African American	**4 (10.8%)**
Asian	**8 (21.6%)**
Ethnicity	
Hispanic or Latino	**1 (2.7%)**
eGFR-MDRD category (mL/min/1.73m2)	
< 60	**11 (29.7%)**
≥ 60	**26 (70.3%)**
Geographic region	
United States	**16 (43.2%)**

Underlying Host Factors:

The target population has changed over time:

	Study 9766-CL-0103	Skiada et al (2011)	Roden et al (2005)
Hematologic Malignancy	22/37 (59%)	102/230 (44%)	154/929 (17%)*
Neutropenia at baseline	10/37 (43%)	N/D	N/D
Bone Marrow Transplant	13/37 (35%)	21/230 (9%)	44/929 (5%)
Diabetes mellitus	4/37 (11%)	39/230 (17%)	337/929 (36%)
Solid Organ Transplant	3/37 (8%)	10/230 (4%)	61/929 (7%)
Solid Organ Malignancy	2/37 (5%)	11/230 (5%)	N/D*
Other	3/37 (8%)	0	0
Aplastic Anemia	1/37 (3%)	4/230 (2%)	N/D
No Underlying Disease	1/37 (3%)	0/230 (0%)	176/929 (19%)
Burn/Trauma	0/37 (0%)	46/230 (20%)	43/176 (24%)

Population Demographics

Pathogen Causing IFD in the mITT-Mucorales Study Population:

	Total (n = 37)
Pathogen	
Mucormycetes NOS	**13 (35.1%)**
***Mucor* NOS**	**7 (18.9%)**
Rhizopus oryzae	**7 (18.9%)**
Rhizomucor	**5 (13.5%)**
Lichtheimia corymbifera	**2 (5.4%)**
***Rhizopus* NOS**	**2 (5.4%)**
Cunninghamella	**1 (2.7%)**

Sites of Infection

Location of Mucormycosis Sites of Infection, Compared to References

Location	Trial 9766-CL-0103 (n = 37)	Roden *et al* (n = 929)	Chamilos *et al* (n = 70)
Lung	22 (59%)	224 (24%)	29 (41%)
Sinus	16 (43%)	359 (39%)	22 (31%)
Disseminated Disease	11 (30%)	25 (3%)	11 (16%)
Eye	7 (19%)	N/D	N/D*
CNS	6 (16%)	87 (9%)	N/D*
Bone	5 (14%)	N/D	N/D
Deep Soft Tissue	3 (8%)	N/D	N/D
GI Tract	2 (5%)	66 (7%)	2 (3%)
Kidneys	2 (5%)	22 (2%)	N/D
Liver	2 (5%)	N/D	N/D
Skin	2 (5%)	176 (19%)	N/D
Spleen	1 (3%)	N/D	N/D

*Rhinoorbitocerebral 6/70 (9%)

Patient Disposition

Primary Reason for Treatment and Study Discontinuation

	Total (n = 37)
Treatment Discontinuation	
Completed	**11 (29.7%)**
Discontinued	**24 (64.9%)**
Primary reason for discontinuation	
Death	11 (29.7%)
Adverse event/intercurrent illness	6 (16.2%)
Did not cooperate	4 (10.8%)
Insufficient therapeutic response	2 (5.4%)
Admin/other	1 (2.7%)
Ongoing Treatment	**2 (5.4%)**

Outcomes

- All Cause Mortality at Day 42 and Day 84

- Data Review Committee Assessment

Primary Outcome

All-Cause Mortality through Day 42 and Day 84
mITT Mucorales Population

Outcome	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
By Day 42				
All-Cause Mortality	**7 (33.3%)**	**5 (45.5%)**	**2 (40.0%)**	**14 (37.8%)**
Deaths	7 (33.3%)	4 (36.4%)	2 (40.0%)	13 (35.1%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)
By Day 84				
All-Cause Mortality	**9 (42.9%)**	**5 (45.5%)**	**2 (40.0%)**	**16 (43.2%)**
Deaths	9 (42.9%)	4 (36.4%)	2 (40.0%)	15 (40.5%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)

DRC Assessed Overall Response

At EOT by Therapy Status

Outcome Response	Primary Therapy (n = 21)[1]	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 35)
Success	6/19 (31.6%)	4/11 (36.4%)	1/5 (20%)	**11/35 (31.4%)**
Complete	3/19 (15.8%)	2/11 (18.2%)	0	5/35 (14.3%)
Partial	3/19 (15.8%)	2/11 (18.2%)	1/5 (20%)	6/35 (17.1%)
Failure	13/19 (68.4%)	7/11 (63.6%)	4/5 (80%)	**24/35 (68.6%)**
Stable	6/19 (31.6%)	2/11 (18.2%)	2/5 (40%)	10/35 (28.6%)
Progression	7/19 (36.8%)	5/11 (45.5%)	2/5 (40%)	14/35 (40%)

[1]Two Patients not assessed due to ongoing treatment

Analysis Strategy: Efficacy

Amphotericin B is the only FDA-approved drug for invasive mucormycosis.

A justification of the non-inferiority margin for amphotericin B was not established

We have therefore concentrated on the benefit of isavuconazonium relative to no treatment at all (Natural history)

Natural History

Study*	Untreated Patients All Cause Mortality (%) [95% Confidence Interval]
Roden *et al*	233/241 (96.7%) [93.6, 98.6]
Skiada *et al*	21/22 (95.5%) [77.2, 99.9]
Fungiscope	29/29 (100%) [88.1, 100.0]
Meta-Analysis	96.2% [94.0, 98.4]

* Includes Post-Mortem Diagnosis

Source: Adapted from Applicant's Information Request Response, November 18, 2014.

Natural History

6-Days Delayed Treatment Doubles Mortality (Chamilos *et al*[1])

Study by Dimitrios Kontoyiannis' group at MD Anderson, Texas, USA

70 Consecutive patients with hematologic malignancy with mucormycosis (1989-2006)

Demographics are similar to Isavuconazonium treatment population:

- 64% Male, Age approximately 50 years
- 41% Pulmonary, 19% Sinus,16% Disseminated, 13% Sinopulmonary
- 40% *Rhizopus* species, 16% *Mucor* species

Outcome:

Delayed amphotericin B–based therapy resulted in a 2-fold increase in mortality rate at 84 Days after diagnosis, compared with early treatment (82.9% vs. 48.6%)

1. Chamilos G., Lewis R.E., Kontoyiannis D.P. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis." Clin Infect Dis. 2008 Aug 15;47(4):503-9

Comparative Analysis

Mortality Rates and 95% Confidence Intervals
Isavuconazonium-Treated Patients Compared to Untreated Patients

Timepoint	ISA Treated Patients All Mucor ACM (%) [95% CI]	ISA Treated Patients Mucor Primary Therapy ACM (%) [95% CI]	6-day delay Chamilos *et al.* ACM (%) [95% CI]	Untreated Patients Mucor Meta-Analysis ACM (%) [95% CI]
Day 42	14/37 (37.8%) [22.5, 55.2]	7/21 (33.3%) [14.6, 57.0]	**82.9% [68.9, 96.8]**	96.2% [94.0, 98.4]
Day 84	16/37 (43.2%) [27.1, 60.5]	**9/21 (42.9%) [21.8, 66.0]**		

Source: Adapted from Applicant's Information Request Response, November 18, 2014.

Isavuconazonium

Overview of Clinical Safety

Isavuconazonium: Overview of Clinical Safety

Outline

- Nonclinical Safety Results
- Summary of Drug Exposure
- Major Safety Results
  - Deaths
  - Nonfatal SAE
  - AE Leading to Discontinuation
- Common AE
- Submission Specific AE
  - Hepatotoxicity
  - Particulate in the IV Formulation
  - QT Segment Shortening
- Drug Class Associated AEs of Interest
  - Hypersensitivity / Infusion Related Reactions

Nonclinical Toxicology

Summary of Safety Studies

Liver Findings:

- Reversible increases in liver weights in mice, rats and monkeys.
- No morphological evidence of hepatocellular damage.
- Isavuconazole induced CYP3A and/or CYP2B

Adrenal Findings: Reversible increase in adrenal weights and/or vacuolation/hypertrophy of adrenocortical cells in monkeys.

Embryo-Fetal Development Findings:

- Skeletal abnormalities in rats and rabbits at one tenth human equivalent systemic exposure.
- Increased rat pup perinatal mortality at one half human equivalent systemic exposure.
- Detected in the milk of lactating dams at concentrations up to 17 fold higher than plasma.

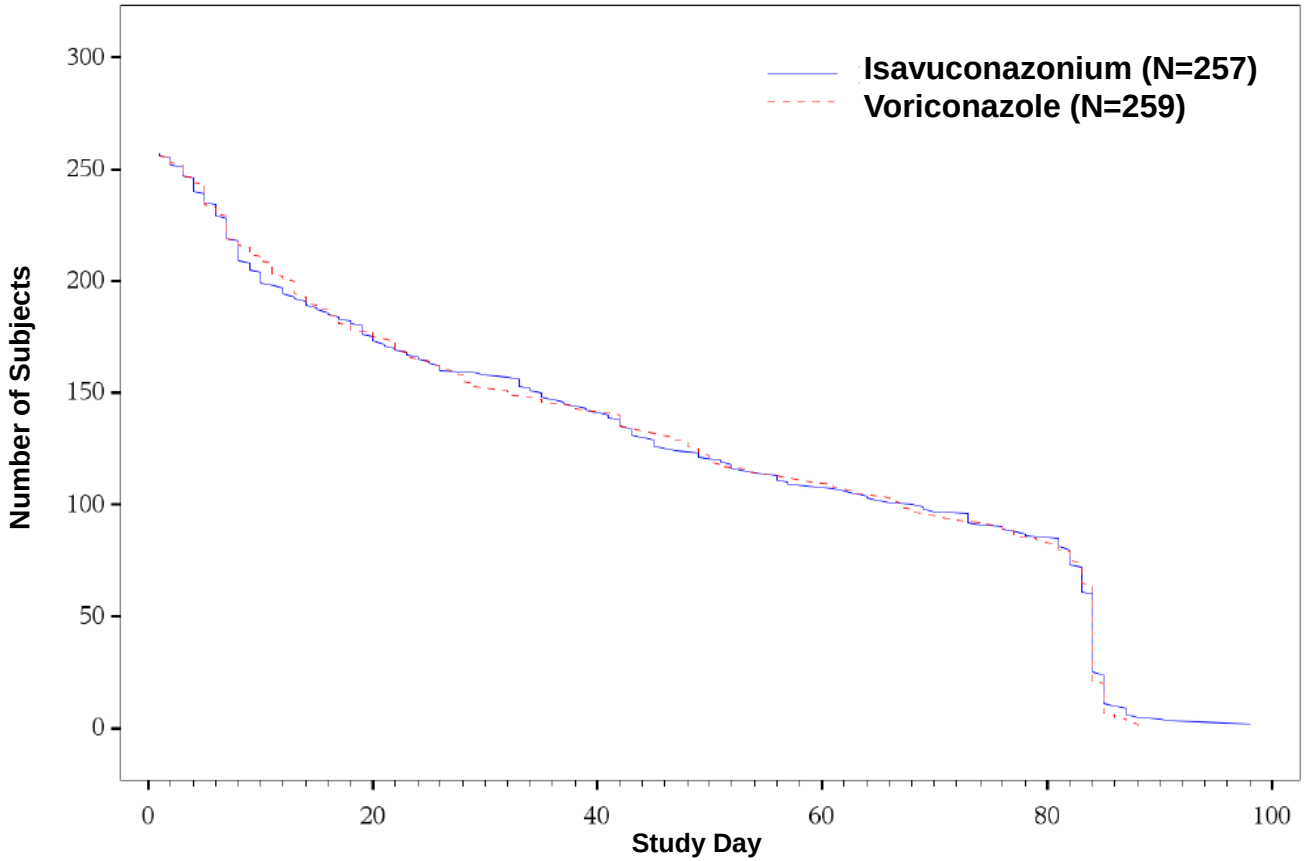
Drug Exposure

Safety Populations in the Isavuconazonium Clinical Development Program

Category	Design	Isavuconazonium (n)	Comparators/ Controls (n)
Integrated 2 and phase 3 trials		547	297
Phase 2 trials		144	38
9766-CL-0101/WSA-CS-001	Comparative	121	38
9766-CL-0102/WSA-CS-002	Non-Comparative	23	0
Phase 3 trials		403	259
9766-CL-0103/WSA-CS-003	Non-Comparative	146	0
9766-CL-0104/WSA-CS-004	**Comparative**	**257**	**259**
Integrated phase 1 trials	Non-Comparative	1001	177
Phase 1 trials completed after the data cutoff date	Non-Comparative	144	0
Renally-impaired subjects	Non-Comparative	24	0
Hepatically-impaired subjects	Non-Comparative	64	0
TOTAL		1692	474

Drug Exposure

Comparative Phase 3 Trial (Study 9766-CL-0104):
Relative Exposure to Study Drug and Comparator by Study Day



Source: Adapted from Applicant's Response, January 6, 2015. Correction of Figure 5, page 40 of briefing document

Deaths

Comparative Phase 3 Trial (Study 9766-CL-0104):
Categorization of Deaths

Category	ISA (n = 257)	VRC (n = 259)
Deaths within 28 days after EOT, TEAE reported	**61**	**69**
Deaths > 28 days after the EOT, TEAE reported	**1**	**3**
Deaths with AE onset reported prior to treatment	14	12
Deaths with no AE reported, > 28 days after EOT	5	3
Total of all known deaths following drug exposure	81	87

Deaths

Comparative Phase 3 Trial (9766-CL-0104):
Treatment Emergent Adverse Events Leading to Death, >5% Frequency

MedDRA v12.1 System Organ Class	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	62 (24%)	72 (28%)
Infections and infestations	28 (11%)	18 (7%)
Respiratory, thoracic and mediastinal disorders	14 (5%)	12 (5%)
Neoplasms benign, malignant and unspecified	10 (4%)	21 (8%)

Serious AE

Comparative Phase 3 Trial (9766-CL-0104):
Serious Treatment Emergent Adverse Events (>2% Frequency)

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	**134 (52.1%)**	**149 (57.5%)**
Respiratory failure	14 (5.4%)	12 (4.6%)
Septic shock	14 (5.4%)	10 (3.9%)
Febrile neutropenia	14 (5.4%)	5 (1.9%)
Pyrexia	8 (3.1%)	10 (3.9%)
Sepsis	7 (2.7%)	8 (3.1%)
Renal failure acute	6 (2.3%)	8 (3.1%)
Pneumonia	5 (1.9%)	10 (3.9%)
Acute myeloid leukemia	3 (1.2%)	8 (3.1%)
Multi-organ failure	1 (0.4%)	7 (2.7%)

Discontinuations

Comparative Phase 3 Trial (Study 9766-CL-0104):
Treatment Emergent Adverse Events Leading to Discontinuation

Fewer isavuconazonium patients (14.4%) than voriconazole patients (22.8%) discontinued study drug due an adverse event.

Notable differences include:
-Hepatobiliary disorders (0.4% vs 2.3%)
-Skin and subcutaneous tissue disorders (0.8% vs 1.9%)
-Psychiatric disorders (0.8% vs 2.3%)

In the Phase 1 healthy volunteer population:
Seven discontinuations occurred in subjects taking suprapharmacologic doses of isavuconazonium (600 mg).

Reasons for discontinuation included AEs of anxiety (3/39), flushing (3/39), headache (3/39), dizziness (2/39) attention disturbances (2/39), nausea (2/39), diarrhea (1/39), and vomiting (1/39)

Common AE

Comparative Phase 3 Trial (Study 9766-CL-0104):
Treatment Emergent Adverse Events ≥ 15% of Patients in Either Treatment Group

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	**247 (96.1%)**	**255 (98.5%)**
Nausea	**71 (27.6%)**	**78 (30.1%)**
Vomiting	**64 (24.9%)**	**73 (28.2%)**
Diarrhea	**61 (23.7%)**	**60 (23.2%)**
Pyrexia	**57 (22.2%)**	**78 (30.1%)**
Hypokalemia	**45 (17.5%)**	**56 (21.6%)**
Headache	**41 (16.0%)**	**38 (14.7%)**
Constipation	**36 (14.0%)**	**54 (20.8%)**

Hepatotoxicity

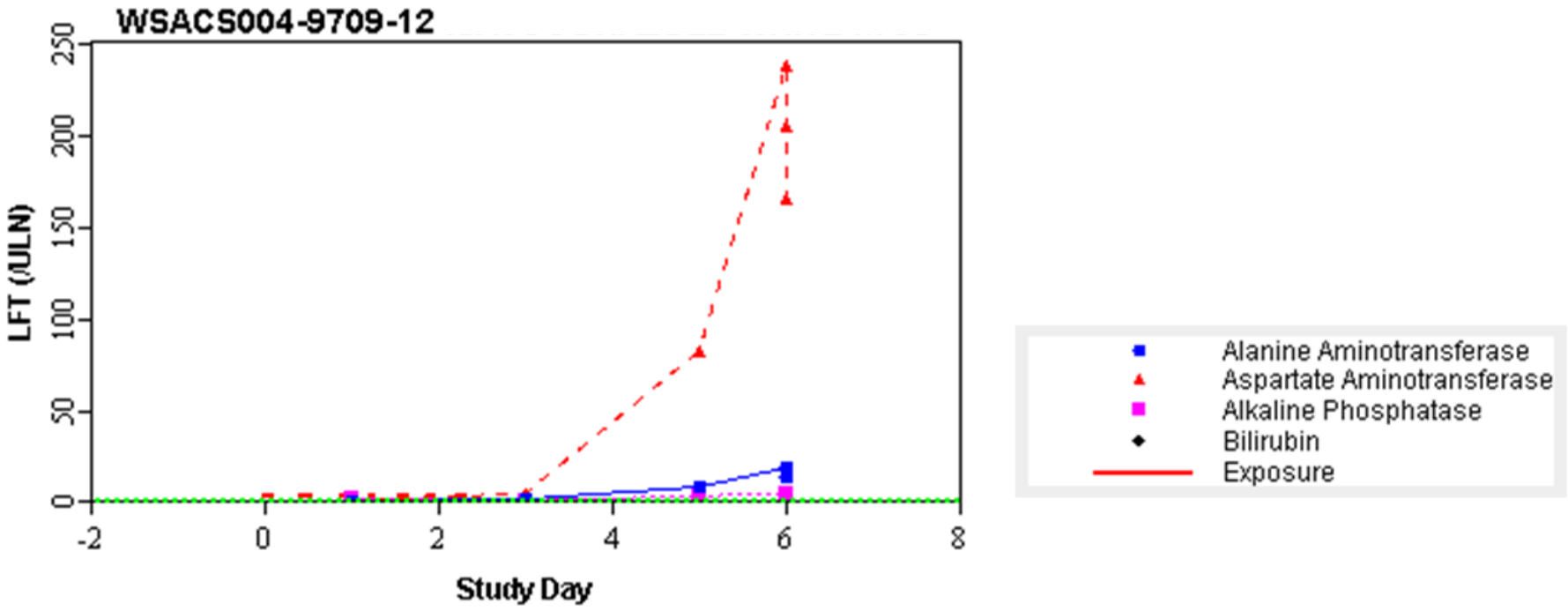
Comparative Phase 3 Trial (Study 9766-CL-0104):
Hepatobiliary TEAEs by Severity and Outcome

MedDRA v12.1 Hepatobiliary System Organ Class	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Any TEAE	**23 (8.9%)**	**42 (16.2%)**
Mild	6 (2.3%)	14 (5.4%)
Moderate	12 (4.7%)	16 (6.2%)
Severe	5 (1.9%)	12 (4.6%)
Serious TEAEs	**3 (1.2%)**	**6 (2.3%)**
TEAEs Leading to Discontinuation	**1 (0.4%)**	**6 (2.3%)**
TEAEs Leading to Death	**1 (0.4%)**	**0**

Acute Hepatic Failure

Study 9766-CL-0104: Subject 9709-12

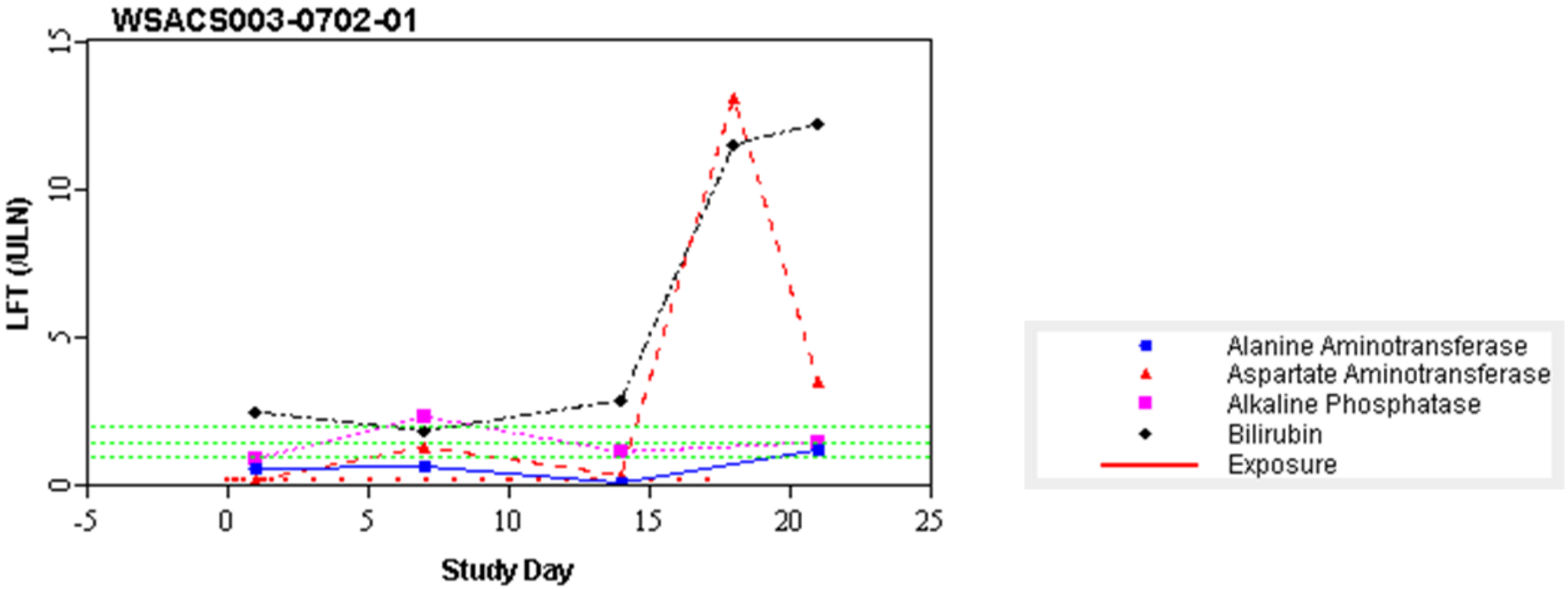
58 year old White male with a history of large B-cell lymphoma, chronic lymphocytic leukemia, and unstaged SCC of the lung, being treated for *Aspergillus fumigatus* pneumonia. Drug discontinued Day 4 due to acute hepatitis (reported Day 5). Days 5-6 ALT and AST rose above 5x ULN. Subject died on Day 6 due to septic shock per investigator. Blood cultures were not positive, and hepatitis serology was not available. Autopsy was not performed. Concomitant medications include acetaminophen. The subject did not have bilirubin values reported, and as such, was not included in the list of subjects that satisfied laboratory criteria for Hy's Law.



Acute Hepatic Failure

Study 9766-CL-0103: Subject 0702-01

28 year old White male with history of chronic hepatitis C, relapsed AML s/p BMT day 223 c/b GVHD treated for *Rhizomucor pusillus* pneumonia with isavuconazonium. Treatment discontinued day 18 due to acute hepatic failure, and patient died from multi-organ failure 5 days later with progression of pneumonia and ongoing hepatic failure. Possible etiologies include activation of chronic hepatitis C, sepsis, AML progression, GVHD, and drug toxicity (isavuconazonium, haloperidol, meropenem, quetiapine, and/or oliclinomel). Patient had ALT or AST > 3xULN and ALP < 2xULN and T-Bili > 2xULN within 3 days apart, thus satisfying laboratory criteria for Hy's Law.



Hepatotoxicity

Comparative Phase 3 Trial (9766-CL-0104): Laboratory Investigations

Investigation	Criteria	Isavuconazonium (n =257)	Voriconazole (n =259)
ALT or AST	> 3 x ULN	39/250 (15.6%)	48/255 (18.8%)
	> 5 x ULN	21/250 (8.4%)	27/255 (10.6%)
	> 10 x ULN	6/250 (2.4%)	14/255 (5.5%)
	> 20 x ULN	4/250 (1.6%)	5/255 (2.0%)
ALP	> 1.5 x ULN	73/249 (29.3%)	98/254 (38.6%)
Total Bilirubin	> 2 x ULN	28/249 (11.2%)	23/255 (9.0%)
Lab Criteria for Hy's Law	(ALT or AST) > 3 x ULN and ALP < 2 x ULN and Total Bilirubin > 2 x ULN	3/251 (1.2%)	7/255 (2.7%)

Particulate in IV Formulation

- A total of 27 subjects received isavuconazonium without a filter.
- No thromboembolic AEs were reported.

AEs Potentially Related to Infusion of Particulate Drug Material:

	9766-CL-0103		9766-CL-0104			
	Isavuconazonium (N = 146)		Isavuconazonium (N = 257)		Voriconazole (N = 259)	
AE	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Pulmonary Embolism (PT)	1	0.7%	0	0	3	1.2%
Embolic and Thrombotic Events (nSMQ)	12	8.2%	9	3.5%	17	6.7%
Pulmonary Hypertension (nSMQ)	0	0	0	0	2	0.8%
Endocarditis (PT)	0	0	1	0.39%	0	0
Infusion Site Reactions (HLT)	3	2.1%	7	2.7%	2	0.8%

QT Segment Shortening

Comparative Phase 3 Trial (9766-CL-0104):

Number and percentage of patients meeting threshold criteria and decreases in QTcF from baseline ECG

QTcF Category	Isavuconazonium (N = 257)	Voriconazole (N = 259)
N	250	252
< 330 msec	5 (2.0%)	5 (2.0%)
< 300 msec	1 (0.4%)	0
N	227	224
Decrease > 60 msec	17 (7.5%)	10 (4.5%)

Hypersensitivity Reactions

Comparative Phase 3 Trial (9766-CL-0104):
Instances of AEs recorded as infusion reactions that could be considered hypersensitivity reactions

1) Patient 004-4910-21 experienced a SAE listed as dyspnea that occurred during infusion. The patient improved with both diuresis and steroids. The study drug, isavuconazonium, was stopped and not reinstated. It is reasonable to consider hypersensitivity as a possible etiology of the SAE.

2) Patient 004-9703-08 discontinued IV isavuconazonium on study Day 2 due to an AE of “allergic dermatitis”, treated with steroids. The investigator considered the reaction probably related to isavuconazonium infusion.

3) Patient 004-5604-01 discontinued isavuconazonium due to severe chills/rigors on infusion Day 11. The adverse reactions recurred on re-challenge the next day. Vital signs were unremarkable. Isavuconazonium was permanently discontinued.

Infusion Reactions

Comparative Phase 3 Trial (9766-CL-0104):
Number and percentage of patients with AE within 2 days of IV dosing that lead to discontinuation

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	8 (3.1%)	6 (2.3%)
Acute respiratory failure	1 (0.4%)	0
Chills	1 (0.4%)	1 (0.4%)
Convulsion	2 (0.8%)	0
Dyspnea	2 (0.8%)	0
Epilepsy	1 (0.4%)	0
Hypotension	1 (0.4%)	0
Respiratory distress or failure	2 (0.8%)	5 (1.9%)

Safety Summary

From the Comparative Phase 3 Trial (9766-CL-0104):
Patients in the Isavuconazonium Treatment Arm Experienced:
-Similar Deaths
-Similar Serious Adverse Events
-Fewer Adverse Events that lead to Study Drug Discontinuation

The Profile of Adverse Events is Consistent with a Drug in the Tri-Azole Class
-Hepatotoxicity
-Hypersensitivity

Safety Concerns Unique to Isavuconazonium include:
-QT segment shortening
-Particulate in the Intravenous Formulation

Acknowledgements

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